PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/00, 9/12

A1

(11) International Publication Number: WO 97/44012

(43) International Publication Date: 27 November 1997 (27.11.97)

(21) International Application Number: PCT/GB97/01309

(22) International Filing Date: 14 May 1997 (14.05.97)

(30) Priority Data: 9610341.1 17 May 1996 (17.05.96) GB

(71) Applicant: ANDARIS LIMITED [GB/GB]; 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB).

(72) Inventors: SMITH, Ian, Joseph; Andaris Limited, 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB). ROGERSON, Cheryl, Vanessa; Andaris Limited, 1 Mere Way, Ruddington, Nottingham NG11 6JS (GB).

(74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

(54) Title: FORMULATION COMPRISING MICROPARTICLES, FOR INHALATION

(57) Abstract

Microparticles, up to 50 μm in size, comprising a therapeutic agent and a surfactant. They can be homogeneously formulated with a HFC propellant.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

FORMULATION COMPRISING MICROPARTICLES, FOR INHALATION

Field of the Invention

This invention relates to a formulation of a drug, in the form of microparticles, suitable for administration by means of a metered dose inhaler.

Background of the Invention

Drugs to be administered to the airways may be formulated dry, for use in a dry powder inhaler, or in a solution or suspension, to be delivered by means of a pressurised metered dose inhaler (pMDI). Suspensions/ formulations of pMDIs typically comprise the drug, micronised to a respirable particle size, surfactant such as oleic acid, lecithin or Span®85, and a propellant. In the past, the propellant has been a chlorofluorocarbon (CFC) such as P11, P12 or P114. CFCs are good solvents for surfactants, but their use involves major environmental concerns. Suitable replacement propellants include the hydrofluoroalkanes HFA134a and HFA227, but the solubility of surfactants in HFAs is poor, and this is reflected in the resulting suspension characteristics.

The solubility of the surfactant in HFAs has been increased by the use of saturated hydrocarbons and alcohols, e.g. ethanol, as disclosed in EP-A-0372777. Alternatively, the surfactant may be adsorbed onto the drug particle surface. However, the surfactant may have limited solubility in the propellant and, in the case of suspension metered dose inhalers, it is then difficult to achieve sufficient adsorption of surfactant onto the drug particle surface to facilitate a controlled flocculation system which is stable.

An object behind the present invention is to avoid the disadvantages of poor surfactant solubility and consequent drug suspension instability described above.

Summary of the Invention

It has now been realised that spray-drying is useful as a means to produce novel drug particles of respirable size range, containing surfactant. This can provide high

local concentrations of surfactant on the surface of the particle, to create the appropriate repulsive forces between particles. More particularly, by balancing the repulsive forces through formulation (i.e. quantity and type of surfactant, pH, etc), when particles are attracted by Van der Waals forces, they are unable to move close together because of electrostatic, steric and entropic repulsive forces. In these circumstances, floccules are formed. The sediment will have a large volume and, because the balancing attractive force is relatively weak, the floccules are easily dispersed.

Microparticles according to this invention comprise a therapeutic agent and a surfactant. The use of spray-drying can provide a product in which the surfactant is uniformly distributed through the matrix of drug and, if necessary or desired, a wall-forming excipient. The microparticles can be formulated with a propellant, e.g. a HFA, for use in a metered dose inhaler.

Description of the Invention

The components used in this invention may all be conventional. Drugs for use in therapy, administered by inhalers, are exemplified in WO-A-9608914. Suitable surfactants include oleic acid, lecithin and sorbitan trioleate as are used in conventional metered dose inhalers. A fuller list of types and examples of suitable surfactants is given in EP-A-0372777, which also describes relevant drugs.

Spray-drying techniques and wall-forming materials (of which HSA, *viz.* human serum albumin, is one example) are described fully in WO-A-9218164 and WO-A-9608914. The materials may be water-soluble, and will generally be predominantly water-soluble, but this may not be essential. These techniques and materials, and the characteristics of the resultant microparticles described therein, are suitable for use in this invention. Thus, for example, the microparticles may be up to 50 μm, e.g. at least 1 μm, and preferably 0.5 to 5 μm in size. They can have a narrow

size range, e.g. more than 90% by mass within the desired range.

In essence, therefore, a surfactant is the additional component in known microcapsules. The amount of surfactant that is used will be chosen with primary regard to the successful formulation of the microparticles in propellant, and all the necessary parameters can be chosen by the skilled man without undue experimentation. Typically, the amount of surfactant will be 0.01 to 15%, preferably at least 0.05%, usually no more than 10%, preferably no more than 5%, and most preferably up to 2.5%, the percentages being by weight based on the weight of the drug. If too little or too much surfactant is present, formulation may be more difficult. The amount of drug in the microcapsules will be chosen with regard to ease of formulation and production, and can readily be determined by one of ordinary skill in the art. The amount of drug in the formulation for inhalation will normally be the same as has previously been used for the desired effect, e.g. up to 250 μg (or more) per actuation of a pMDI.

The following Examples illustrate the invention.

Examples

Salbutamol sulphate was chosen as a model drug substance, and microparticles were formed using three surfactants commonly used in pMDIs, i.e. lecithin, oleic acid and sorbitan trioleate. The range of surfactant to drug was from 0.05 to 5% w/w.

The current marketed pMDIs of salbutamol contain 100 μg salbutamol base equivalent per actuation. However, a typical range of dose per actuation across pMDI products covers 25-250 μg per actuation, although this can be much more. In this study, formulations were therefore prepared at 25, 125 and 250 μg per actuation, in plastic coated bottles, with HFA134a or HFA227.

These were assessed by visual examination on initial preparation and after six months storage at 20°C. In particular, differential flocculation behaviour between

differing levels of surfactant, and signs of headspace and wall drug deposition after storage, were examined.

Samples of 125 μg product with HFA134a propellant and oleic acid were also examined for priming behaviour, single shot drug delivery, fine particle dose, and expiry dosing behaviour.

Batches of microcapsules were prepared in a minispray drier. The key process parameters are given in Tables A1 (using oleic acid), A2 (using sorbitan trioleate) and A3 (lecithin).

Table A1

Total solids (% w/v)	Oleic acid (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	0	66	66
24.1	0.25	0	70	70
24.2	0.5	5	63	63
24.3	1.25	5	62	60
24.6	2.5	5	65	68
24.8	3.75	10	62	64
25.1	5	15	70	75

Table A2

Total solids (% w/v)	Sorbitan Trioleate (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	10	68	71
24.1	0.25	10	69	72
24.2	0.5	10	70	74
24.3	1.25	10	69	72
24.6	2.5	10	69	72
24.8	3.75	15	70	73
25.1	5	20	71	75

Table A3

Total solids (% w/v)	Lecithin (% w/w of drug)	Ethanol (% v/v)	Outlet Temp. start of run (°C)	Outlet Temp. end of run (°C)
24.1	0.05	10	66	68
24.1	0.25	10	61	65
24.2	0.5	10	68	72
24.3	1.25	10	69	71
24.6	2.5	10	77	78
24.8	3.75	15	73	73
25.1	5	15	72	76

The total solids content of the spray-drying solution ranged from 24.1-25.1% w/v, depending upon the surfactant level. To achieve solution of the higher levels of surfactant, ethanol was added to the spray-dry feedstock as a cosolvent. An inlet temperature of 140°C and a solution feed rate of 4 g per minute was employed for all batches. The feedstock was kept under nitrogen.

The prepared microcapsules were examined microscopically. From photomicrographs, the microcapsules appeared of similar size for all batches. The microcapsules were also sized using a Coulter LS, after suspension in acetone and sonication.

The mean volume median diameter of the microcapsules was 4.3 μm (range 3.8-4.8). If a smaller sized microparticle is desired, for pMDI formulation, the total solids content of the spray-dry feedstock should be reduced.

Pressurised metered dose inhalers were prepared in plastic-coated glass bottles, closed with Bespak BK357 valves, of 50 μl nominal metering volume. The appropriate weight of microcapsules was placed in the bottle (5, 25 or 50 mg for 25, 125 and 250 μg per actuation, respectively)

and 12 g HFA134a or 14.1 g HFA227 added. This gave a nominal 200 actuations per bottle.

One week after manufacture each series of bottles was shaken, then placed against a black background and allowed to settle. Photographs were taken immediately and also 1 minute, 10 minutes, 30 minutes, 20 hours and 1 week after shaking. Tables B1 and B2 give the turbidity scores after 30 minutes settling for HFA134a and HFA227, respectively. The turbidity of the samples was scored on a 0 to +++++ scale, where 0 represents a completely clear supernatant and +++++ the most turbid supernatant. The HFA134a suspensions gave a greater degree of differential settling behaviour across the series compared to HFA227 suspensions.

Table B1

Surfactant	Surfactant concentration (% w/w of drug)						
	0.05	0.1	0.5	1.25	2.5	3.75	5
Oleic acid	++++	+++	++	+++	+++++	++	+
Span 85	++++	++++	++	+++++	++	+	0
Lecithin	+++	+++	++	+++++	++++	++	++++

Table B2

Surfactant	Surfactant concentration (% w/w of drug)						
	0.05	0.1	0.5	1.25	2.5	3.75	5
Oleic acid	+++	++	++	++	++	+	++
Span 85	+++	++	+++	+++	+	++	0
Lecithin	+++	+++	+++	+++	+++	+++	+++

To have particles remaining in suspension after 30 min. is indicative of good physical stability in such systems. Turbid solutions will generally perform better.

The 125 μg salbutamol/oleic acid formulations containing 0.05, 0.5, 1.25, 2.5 and 5% w/w surfactant were examined according to the following regime:

Actuation Number	Test
1 to 8	Single actuation assay - priming data
9 to 10	Fire to waste
11 to 19	Multistage liquid impinger
15 to 95	Fire to waste
96 to 100	Single actuation assay
101 to 149	Fire to waste
150 to 159	Multistage liquid impinger
160 to exhaustion	Determine shot weight and single actuation assays to exhaustion

The actuator used in these tests was supplied by Bespak and had a jet orifice diameter of 0.53 mm.

The drug actuation and shot weight results for actuations 1 to 8 are shown in Figure 1, which is a plot of salbutamol ex-actuator (0-400 μg) against shot number (1 to 8). On the graph, ♦ represents 0.05%, ■ represents 0.5%, ▲ represents 1.25%, x represents 2.5%, and * represents 5%. As would be expected, the first actuation for each sample gave a low shot weight and corresponding low ex-actuator drug content. The samples which had shown the most turbid supernatants on visual examination (0.05% and 2.5%) displayed the most consistent dosing near to target.

The drug content per actuation has been examined for individual actuations 1 to 8 and 96 to 100. These data can be used as a measure of dose uniformity. The actuator deposition across the samples ranged from 6.4 to 34.9 μg, i.e. 5-28% of the target dose, after exclusion of actuations 1 to 3 as priming shots. As the main aim of this study was to compare different formulations, the

variability of the total dose was believed to be a better comparator.

Figure 2 is a graph of % coefficient of variation (0-60) against % oleic acid (0.05-5). Figure 3 is a graph of the range of salbutamol per actuation (0-400 μg) against % oleic acid (0.05-5). The 0.5% formulation, having the highest turbidity score, gave uniform dosing.

The size distribution of the drug emitted from the pMDI was assessed using an Astra Draco multi-stage impinger. The four stages of the impinger have cut-off diameters of 1.7, 3.1, 6.8 and 13.4 μm at 60 litre per minute air flow. The size distribution was assessed at the beginning of the pack (actuations 11 to 20) and towards the end of the pack (actuations 150 to 159). For the 0.05, 0.5, 1.25% w/w oleic acid samples, the distributions are similar at the beginning and end of the pack.

The drug per actuation for the 5.0% w/w oleic acid formulation is markedly different between the beginning and end of the pack (286 μg and 88 μg, respectively). The shape of the distributions also differs, suggesting that the drug discharged at the end of the pack is of larger size than that discharged at the start of the pack.

In a study of doses to exhaustion, the fall in shot weight was followed from actuation 160 and, after a 10% fall in shot weight was observed, the drug per actuation was determined. The results for drug per actuation through the use of the pack are shown in Figures 4 to 8.

Figures 4 to 8 are each graphs, respectively for 0.05, 0.5, 1.25, 2.5 and 5% oleic acid, of salbutamol ex-actuator (μg) against shot number. ♦ represents ex-actuator and ■ represents shot weight, in each case.

CLAIMS

1. Microparticles, up to 50 μm in size, comprising a therapeutic agent and a surfactant.

2. Microparticles according to claim 1, comprising also a wall-forming material.

3. Microparticles according to claim 1 or claim 2, whose components are at least predominantly water-soluble.

4. Microparticles according to any preceding claim, 0.5 to 10 μm in size.

5. Microparticles according to any preceding claim, obtainable by spray-drying.

6. A homogeneous formulation of microparticles according to any preceding claim and a propellant.

7. A formulation according to claim 6, wherein the propellant is a hydrofluorocarbon.

8. A metered dose inhaler comprising a formulation according to claim 6 or claim 7.

Fig.1.

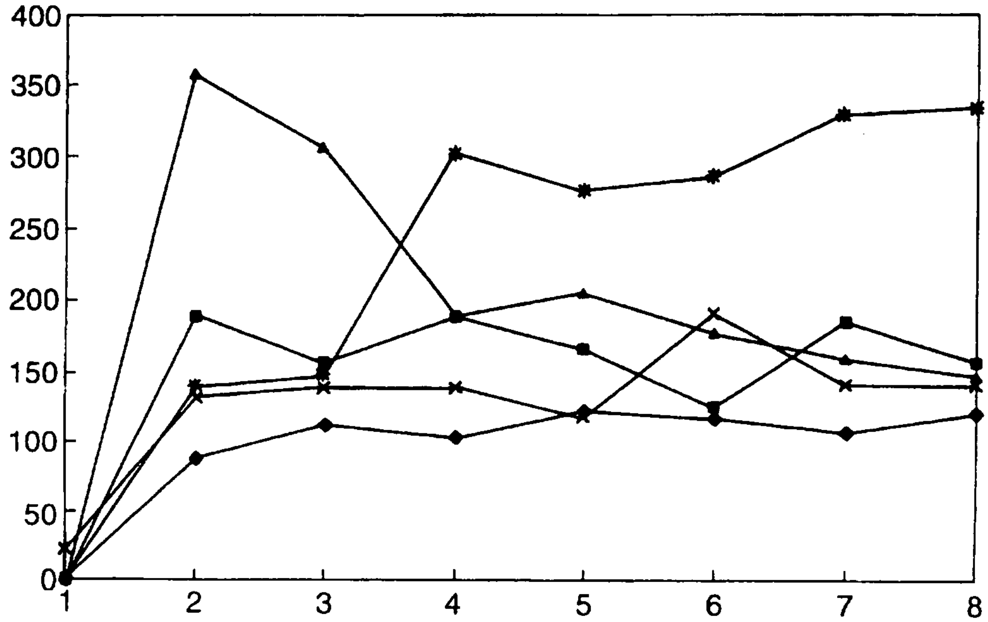

400
350
300
250
200
150
100
50
0
1
2
3
4
5
6
7
8

Fig.2.

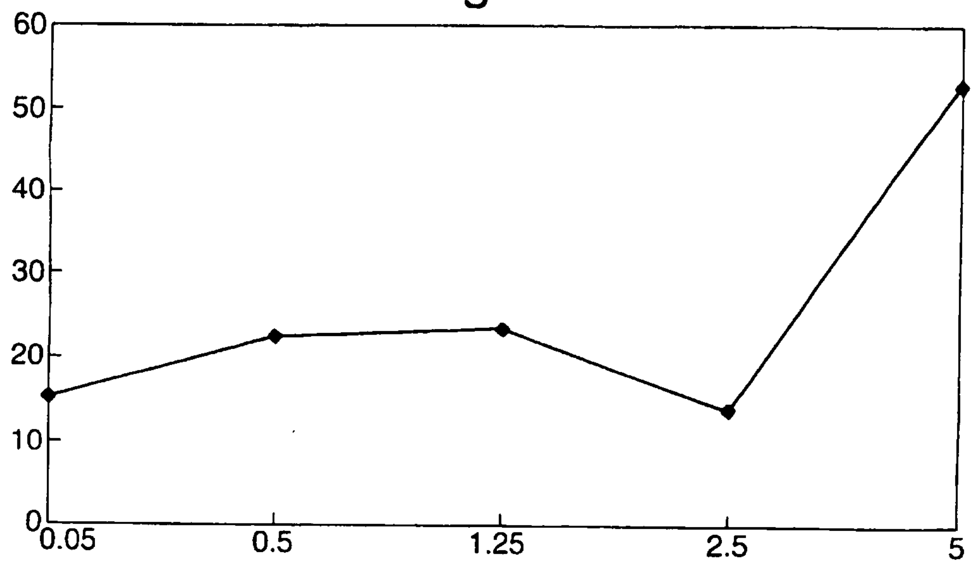

60
50
40
30
20
10
0
0.05
0.5
1.25
2.5
5

Fig.3.

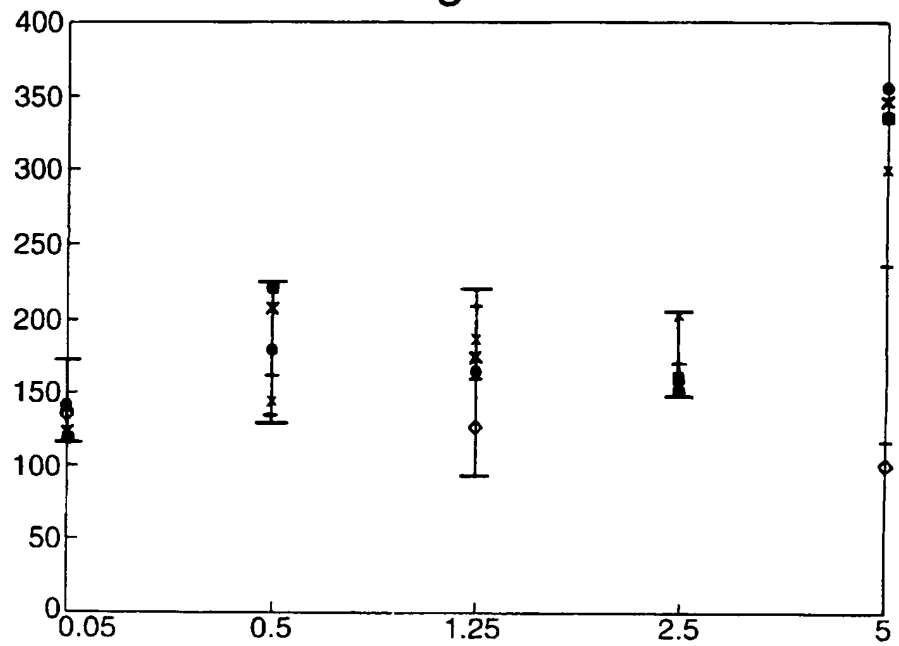

400
350
300
250
200
150
100
50
0
0.05
0.5
1.25
2.5
5

Fig.4.

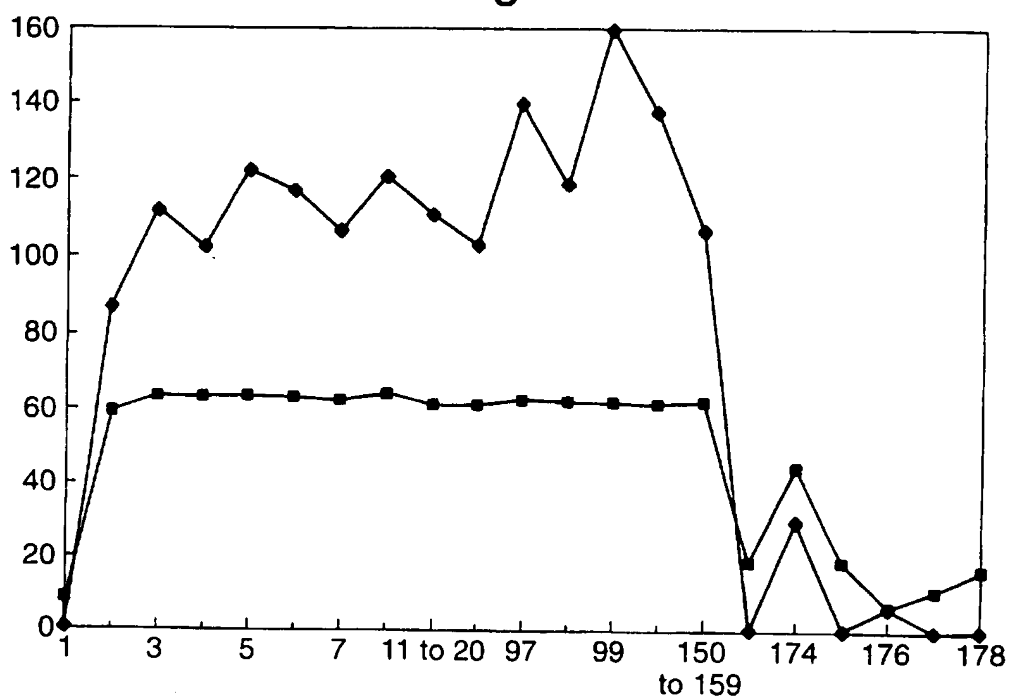

160
140
120
100
80
60
40
20
0
1
3
5
7
11 to 20
97
99
150 to 159
174
176
178

Fig.5.

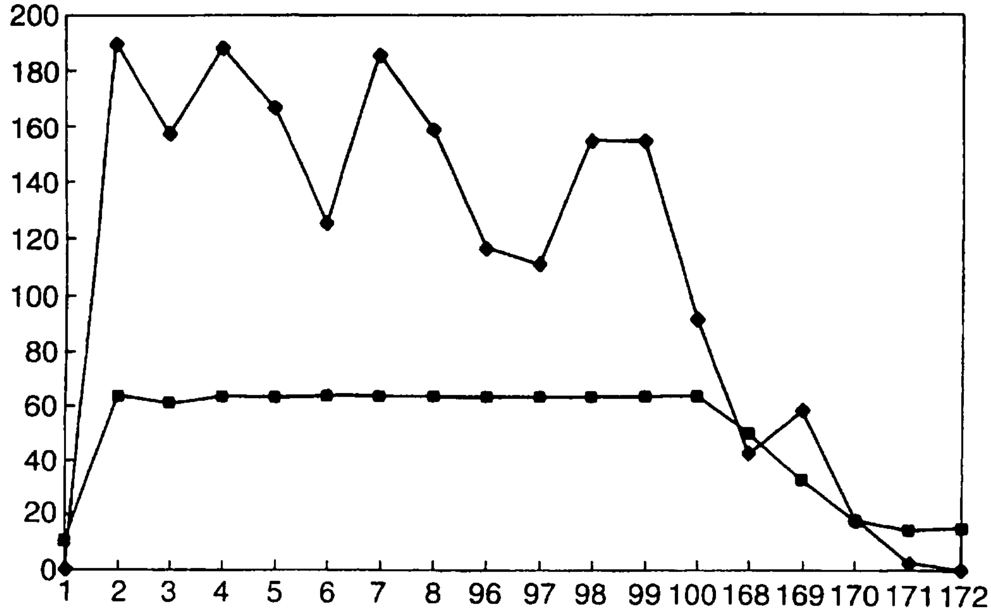

200
180
160
140
120
100
80
60
40
20
0
1 2 3 4 5 6 7 8 96 97 98 99 100 168 169 170 171 172

Fig.6.

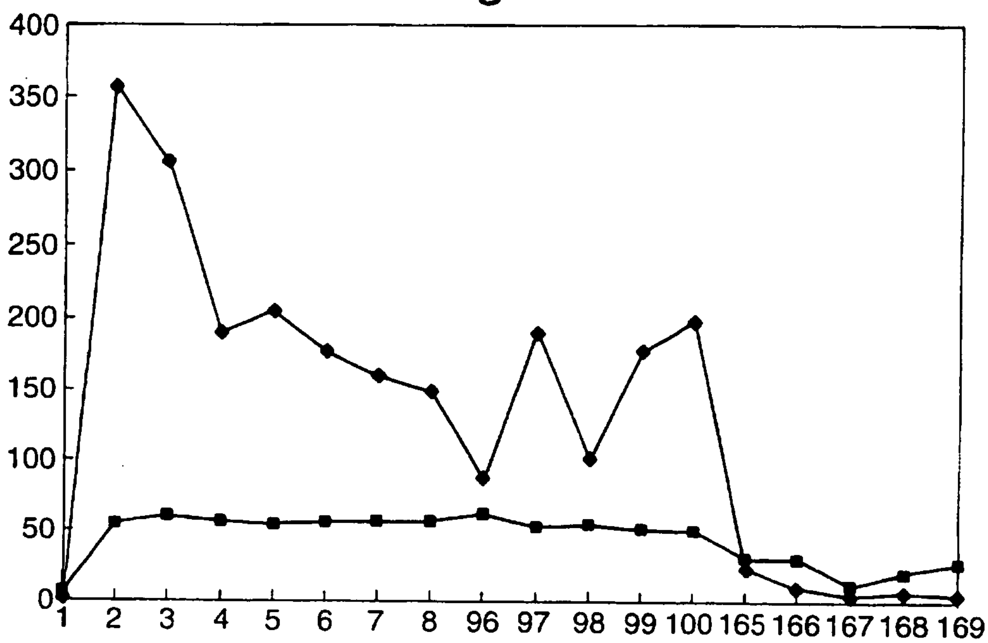

400
350
300
250
200
150
100
50
0
1 2 3 4 5 6 7 8 96 97 98 99 100 165 166 167 168 169

Fig.7.

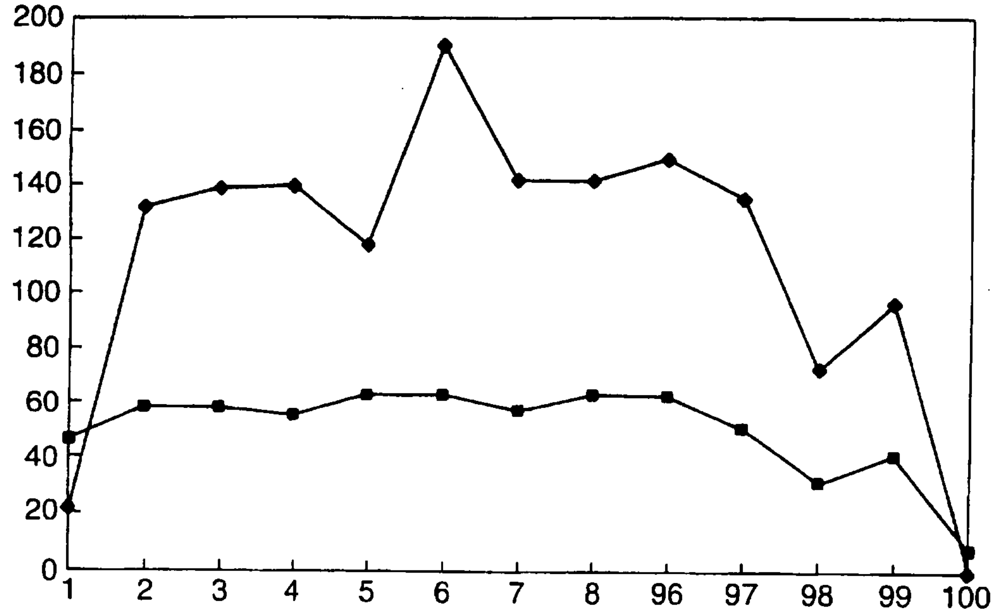
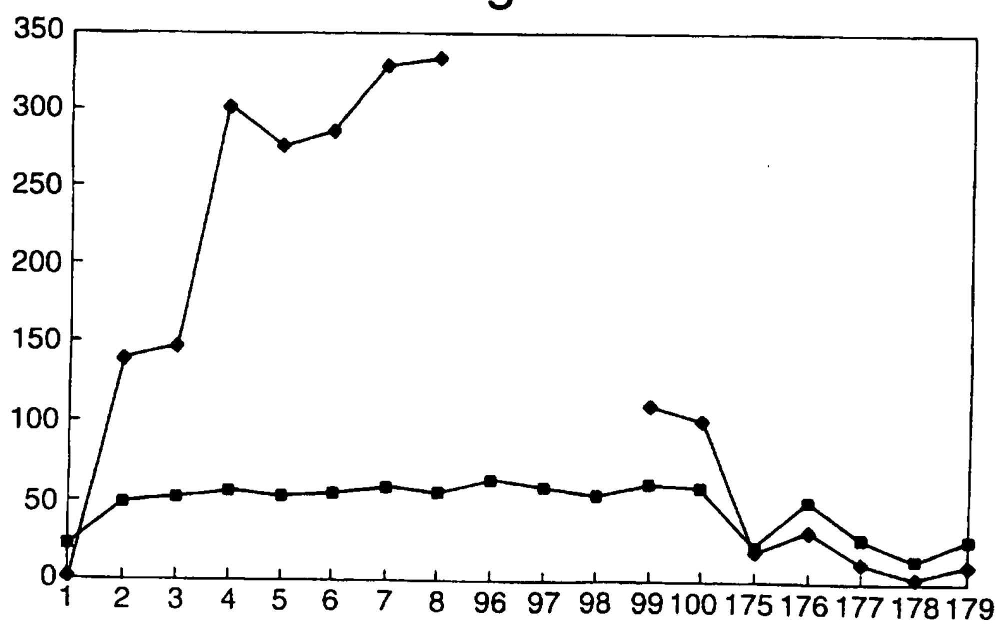

200
180
160
140
120
100
80
60
40
20
0
1
2
3
4
5
6
7
8
96
97
98
99
100

Fig.8.


350
300
250
200
150
100
50
0
1
2
3
4
5
6
7
8
96
97
98
99
100
175
176
177
178
179

INTERNATIONAL SEARCH REPORT

Intern[illegible]al Application No
PCT/GB 97/01309

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 09814 A (ANDARIS LIMITED) 4 April 1996 cited in the application see claims 1-6,12 ---	1-5
X	WO 95 27476 A (THE CENTER FOR INNOVATIVE TECHNOLOGY) 19 October 1995 see claim 1 see page 1, line 25 - page 2, line 16 see page 2, line 31 - page 3, line 1 ---	1,4,6-8
X	EP 0 372 777 A (RIKER LABORATOIRES INC.) 13 June 1990 cited in the application see claims 1-4	1,3,4,6, 7
Y	---	2,5
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 1997	08.09.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Alvarez Alvarez, C

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 97/01309

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 681 843 A (ANDARIS LIMITED) 15 November 1995 see claims 1-4,7,11-14 & WO 92 18164 A cited in the application ---	2,5
X	WO 95 31964 A (GLAXO AUSTRALIA PTY. LIMITED ET AL.) 30 November 1995 see claims 1,2 -----	1,4

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/GB 97/01309

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9609814 A	04-04-96	AU 3530295 A	19-04-96
		CA 2199954 A	04-04-96
		EP 0783298 A	16-07-97
		FI 971332 A	01-04-97
		NO 971438 A	26-03-97
WO 9527476 A	19-10-95	US 5508023 A	16-04-96
		CA 2187447 A	19-10-95
		EP 0755247 A	29-01-97
EP 372777 A	13-06-90	AU 631155 B	19-11-92
		AU 4595689 A	14-06-90
		CA 2004598 A	06-06-90
		DE 68924540 D	16-11-95
		DE 68924540 T	15-05-96
		EP 0499344 A	19-08-92
		EP 0653204 A	17-05-95
		ES 2045470 T	16-01-94
		ES 2077971 T	01-12-95
		HK 7196 A	26-01-96
		IL 92457 A	21-10-94
		JP 2200627 A	08-08-90
		US 5225183 A	06-07-93
EP 681843 A	15-11-95	AU 655016 B	01-12-94
		AU 1589192 A	17-11-92
		AU 7448394 A	22-12-94
		CN 1066977 A	16-12-92
		EP 0512693 A	11-11-92
		EP 0533886 A	31-03-93
		WO 9218164 A	29-10-92
		GB 2260745 A,B	28-04-93
		NZ 242328 A	22-12-94
		US 5518709 A	21-05-96
WO 9531964 A	30-11-95	AU 2614595 A	18-12-95
		CA 2190763 A	30-11-95
		EP 0760649 A	12-03-97
		FI 964634 A	20-11-96
		NO 964938 A	20-11-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 97/01309

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9531964 A		PL 317225 A	17-03-97
		ZA 9504101 A	29-01-96

Form PCT/ISA/210 (patent family annex) (July 1992)